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A systematic review of the effect of cannabidiol on cognitive function: relevance to schizophrenia

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Abstract
Background and objectives Cognitive impairment is a core symptom domain of schizophrenia, neurological disorders and substance abuse. It is characterised by deficits in learning, memory, attention and executive functioning and can severely impact daily living. Antipsychotic drugs prescribed to treat schizophrenia provide limited cognitive benefits and novel therapeutic targets are required. Cannabidiol (CBD), a component of the cannabis plant, has anti-inflammatory and antipsychotic-like properties; however, its ability to improve cognitive impairment has not been thoroughly explored. The aim of this systematic review was to evaluate preclinical and clinical literature on the effects of CBD in cognitive domains relevant to schizophrenia. Methods A systematic literature search was performed across numerous electronic databases for English language articles (January 1990-March 2016), with 27 articles (18 preclinical and 9 clinical studies) included in the present review. Results CBD improves cognition in multiple preclinical models of cognitive impairment, including models of neuropsychiatric (schizophrenia), neurodegenerative (Alzheimer's disease), neuro-inflammatory (meningitis, sepsis and cerebral malaria) and neurological disorders (hepatic encephalopathy and brain ischemia). To date, there is one clinical investigation into the effects of CBD on cognition in schizophrenia patients, with negative results for the Stroop test. CBD attenuates Δ^9-THC-induced cognitive deficits. Conclusions The efficacy of CBD to improve cognition in schizophrenia cannot be elucidated due to lack of clinical evidence; however, given the ability of CBD to restore cognition in multiple studies of impairment, further investigation into its efficacy in schizophrenia is warranted. Potential mechanisms underlying the efficacy of CBD to improve cognition are discussed.

Keywords
function:, relevance, schizophrenia, systematic, effect, review, cannabidiol, cognitive

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Title: A systematic review of the effect of cannabidiol on cognitive function: Relevance to schizophrenia

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Abstract

Background and Objectives: Cognitive impairment is a core symptom domain of schizophrenia, neurological disorders and substance abuse. It is characterised by deficits in learning, memory, attention and executive functioning and can severely impact daily living. Antipsychotic drugs prescribed to treat schizophrenia provide limited cognitive benefits and novel therapeutic targets are required. Cannabidiol (CBD), a component of the cannabis plant, has anti-inflammatory and antipsychotic-like properties; however, its ability to improve cognitive impairment has not been thoroughly explored. The aim of this systematic review was to evaluate preclinical and clinical literature on the effects of CBD in cognitive domains relevant to schizophrenia.

Methods: A systematic literature search was performed across numerous electronic databases for English language articles (January 1990 to March 2016), with 27 articles (18 preclinical and 9 clinical studies) included in the present review.

Results: CBD improves cognition in multiple preclinical models of cognitive impairment, including models of neuropsychiatric (schizophrenia), neurodegenerative (Alzheimer's disease), neuro-inflammatory (meningitis, sepsis and cerebral malaria) and neurological disorders (hepatic encephalopathy and brain ischemia). To-date, there is one clinical investigation into the effects of CBD on cognition in schizophrenia patients, with negative results for the stroop test. CBD attenuates Δ^9-THC-induced cognitive deficits.

Conclusions: The efficacy of CBD to improve cognition in schizophrenia cannot be elucidated due to lack of clinical evidence; however, given the ability of CBD to restore cognition in multiple studies of impairment, further investigation into its efficacy in schizophrenia is warranted. Potential mechanisms underlying the efficacy of CBD to improve cognition are discussed.

1 Introduction

Since the introduction of 'third generation' atypical antipsychotics in the 1990s, there have been relatively few clinically significant advances in treatment options for patients suffering from affective and non-affective psychotic disorders such as schizophrenia and bipolar disorder [1]. Antipsychotics have therapeutic efficacy in treating some of the positive (hallucinations, delusions) and negative (anhedonia, apathy) symptoms of schizophrenia; however, they are limited in their ability to treat the cognitive domain of the disease [2]. Cognitive impairment is a core symptom underlying many neuropsychiatric disorders. Approximately 75-85% of people with schizophrenia experience deficits in cognition that negatively impact day-to-day living, including the ability to maintain employment, relationships and self-care [3]. Cognitive deficits often precede the emergence of other symptoms in schizophrenia, are associated with poor medication compliance and a higher tendency for relapse in first episode psychosis [4]. In fact, cognitive deficits are considered a better prognostic indicator in schizophrenia patients than other symptom domains because the severity of cognitive dysfunction correlates with earlier disease onset [2] and can predict clinical course and future functional outcomes [5]. As current antipsychotic medications show minimal benefits for cognitive impairment [2] and have adverse side-effects (such as weight gain and motor disturbances) [6], there is an urgent requirement to identify new pharmacological treatments that can enhance cognitive function and improve the overall quality of life for people with schizophrenia. In an effort to address cognitive dysfunction in schizophrenia, the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative was developed that identifies 7 primary cognitive domains as targets for treatment in schizophrenia [2]. These domains include processing speed, verbal learning and memory, attention and vigilance, reasoning and problem solving, visual learning and memory, social cognition and working memory [2]. The authors [2] recommend that preclinical studies assessing the efficacy and functional outcomes of new pharmacological treatments in schizophrenia models should use behavioural tests that examine domains identified in MATRICS. Likewise, the MATRICS Consensus Cognitive Battery (a battery of 10 tests that examine the MATRICs cognitive domains) should be used in clinical trials that assess the efficacy of potential cognitive-enhancing drugs for schizophrenia, to ensure standardised testing and maximise reproducibility between trials [2].

Cannabis sativa is the most widely used drug in the world and contains over 70 different constituents, including delta-9-tetrahydrocannabinol (Δ^9-THC) and cannabidiol (CBD) [7]. Compared to the general population, individuals with schizophrenia are twice as likely to consume cannabis, with evidence of worsened psychotic

symptoms and a higher incidence of relapse and poor treatment outcomes in users [7]. Cannabis use during adolescence is a well-documented risk factor for developing schizophrenia and lowers the age of symptom onset [8]. Cannabis interacts with the endogenous cannabinoid system and alterations in endogenous cannabinoid signalling have been observed in patients with schizophrenia. For example, studies report elevated levels of the endogenous cannabinoids anandamide (AEA) and 2-arachidonyl glycerol (2-AG) in cerebrospinal fluid and blood samples of patients [9-13], while post-mortem brain tissue and neuroimaging studies report elevations in cannabinoid CB1 receptor density in brain regions implicated in cognition, in people with schizophrenia [14-16]. Interestingly, Δ^9-THC administration induces symptoms in healthy volunteers that resemble psychosis, including hallucinations, delusions, depersonalisation and emotional lability, coupled with cognitive impairment in learning and memory domains [7]. On the other hand, initial observations in the 1970s suggested that the cannabis constituent CBD interferes with the detrimental actions of Δ^9-THC in terms of psychotic proneness and cognitive dysfunction [17]. Indeed, more recent studies have identified an inverse relationship between CBD content in cannabis strains and the prevalence of psychotic symptoms, such as hallucinations and delusions, suggesting a possible protective effect of CBD [18, 19]. Furthermore, clinical and preclinical studies spanning more than a decade [13, 20-23], demonstrate potential for CBD as an antipsychotic agent against the positive and negative symptoms of schizophrenia (as reviewed in [24]). Despite these findings, evidence of the efficacy of CBD to improve cognitive deficits associated with schizophrenia has not been thoroughly explored. CBD is a particularly interesting target as a novel approach to improving cognition in schizophrenia, in part, due to its strong anti-inflammatory properties [25]. Inflammation, particularly maternal immune activation during pregnancy, is a strong risk factor for schizophrenia pathogenesis and has been linked to the severity of cognitive deficits experienced by individuals [4]. Furthermore, immune system dysfunction has been reported in first episode and antipsychotic-treated schizophrenia patients, implicating this system in the pathogenesis of schizophrenia and as a potential therapeutic target for its treatment [4, 26].

The aim of the present paper was to provide a detailed systematic literature review of existing preclinical and clinical research examining the effects of CBD on the cognitive domains relevant to schizophrenia, as identified by MATRICS [2]. Research papers included in this review were subdivided into the following categories: 1) studies that examined the ability of CBD to treat cognitive impairment in neuropsychiatric conditions and other neurological disorders, 2) studies that investigated the impact of CBD on cognitive measures during a cannabis or Δ^9-THC challenge, or in a healthy state, and 3) studies that examined the effects of CBD in inflammatory-

based preclinical models of cognitive impairment. Finally, the potential mechanisms of CBD's action on cognitive function, as well as recommendations for future research are discussed.

2 Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and reporting criteria [27]. The number of studies retained and omitted for this systematic review was recorded for each of the screening stages according to the PRISMA Statement (Figure 1) [27].

2.1 Search Strategy

A literature search was performed using electronic databases (MEDLINE, Web of Science and Scopus) for original, published, English-language research articles, with publication dates spanning from January 1990 to March 2016. Key words included cannabidiol, cognition, cognitive impairment, memory and learning. Different combinations of search terms were used based on the requirements or limitations of each database. For example, the search strategy for Medline was (cannabidiol AND cognition) or (cannabidiol AND cognitive AND impairment). The reference lists of eligible studies were also screened to identify additional studies.

2.2 Eligibility Criteria

Studies eligible for inclusion in this systematic review must have assessed the effect of CBD on cognitive domains relevant to schizophrenia (as defined in MATRICS) and must have been published in English. All studies were initially screened by title and abstract to ensure that only empirical studies related to the topic were included. Original research articles that passed the initial screening were reviewed in full text. Studies were further excluded that: (1) did not test cognitive domains related to MATRICS, used self-reporting measures to generate cognitive scores or focused on other outcomes (e.g. reward/motivation, anxiety), or (2) used standardised cannabis extracts containing both Δ^9-THC and CBD, such as oromucosal sprays (Sativex®), without appropriate controls (i.e. Δ^9-THC or CBD only groups) to assess the effects of CBD alone.

2.3 Data Extraction and Analysis

Following the screening process, original research articles that fit the criterion were further reviewed and the following information was extracted: author, year of publication, journal of publication, aim of the research,

sample size, gender, drugs administered and dosage, as well as species and strain for preclinical studies. In addition, details of the CBD intervention were recorded, including the dose, frequency and route of administration, experimental paradigm used, as well as information pertaining to treatment outcomes, such as cognitive tests used (either clinical or behavioural), results of the cognitive testing, results of any biochemical analyses relating to cognition, and the overall conclusion of the research. The detailed information was tabulated and partitioned according to clinical or preclinical research (Tables 1 and 2, respectively).

3 Literature Search Results

The initial search strategy yielded a total of 75 articles from Medline (22 articles), Scopus (25 articles) and Web of Science (28 articles). Duplicate publications were excluded, yielding a total of 39 articles that were screened by title and abstract for eligibility. Nine studies were excluded because they did not use behavioural or clinical tests to assess cognition in the domains identified by MATRICS, they generated cognitive scores through self-reported data or they did not report data from cognitive testing (Supplementary Table 1). Two studies investigating the effects of cannabis, and two studies investigating the effects of Sativex®, were excluded as they either lacked adequate control groups (either Δ^9-THC or CBD only groups) to ascertain the effects of CBD alone, or did not report CBD content (Supplementary Table 1). A total of 27 studies passed the screening process and were collated for qualitative synthesis (Tables 1 and 2), including 9 clinical (human) studies (consisting of 1 double-blind, placebo-controlled trial; 1 randomised, double-blind, placebo-controlled trial; 1 double-blind, placebo-controlled, cross-over trial; 4 randomised, double-blind, placebo-controlled, cross-over trials and 2 naturalistic, cross-over study designs) and 18 preclinical studies (including 11 mouse, 6 rat and 1 non-human primate models). The clinical studies investigated the effects of CBD on: (1) verbal, episodic and recognition memory in cannabis users using naturalistic study designs (n=2); (2) working and social recognition memory, attention, verbal learning and memory and executive function using standardised cannabis extract or Δ^9-THC challenge paradigms in non-users and cannabis users (n=6); and (3) selective attention in schizophrenia patients (n=1). The preclinical studies included in this review investigated the effects of CBD on cognition in (1) neuropsychiatric modelling of schizophrenia and Alzheimer's disease (n=6); (2) cannabis and Δ^9-THC challenge paradigms and healthy rodents (n=4); (4) neurological conditions, such as brain ischemia, hepatic encephalopathy, as well as pain (n=5); and (4) inflammation-based models of cognitive impairment (n=3). Domains assessed by the preclinical studies aligned with the cognitive domains described in MATRICS and included working memory, object recognition and social recognition memory, associative learning, procedural

and declarative memory, and spatial learning and memory. In the present review, the literature pertaining to the effect of CBD on cognitive impairment in pathological states is presented separately to the literature examining the effects of CBD on cognition in drug-induced and healthy states.

3.1 Cannabidiol as a therapeutic intervention for cognitive impairment in neuropsychiatric and neurodegenerative disorders

3.1.1 Effects of CBD on cognitive function in schizophrenia

There has been limited examination of the clinical efficacy of CBD to treat cognitive dysfunction in neuropsychiatric disorders, with one published study that examined effects in psychiatric patients [28] (Table 1) and two studies that utilised a preclinical model of schizophrenia in rodents [29, 30] (Table 2). A study conducted by Hallak et al [28] investigated the therapeutic efficacy of CBD to improve cognitive deficits in patients with schizophrenia. Testing comprised of two sessions, the first of which subjected participants to a Stroop Colour Word test, followed by a second session (one month later) where participants were administered a single dose of CBD (300 mg or 600 mg) or placebo then performed the Stroop Colour Word test one-hour post-treatment, in order to assess the effects of CBD on selective attention [28]. The number of errors made in the Stroop Colour Word test significantly decreased between testing sessions in both the 300 mg CBD-treated and the placebo groups, with a similar trend observed in the 600 mg CBD-treated group [28]. The improvement across all experimental groups, particularly the placebo-treated group, is indicative of a learning effect rather than a treatment effect; the authors attributed the learning effect to the short (one month) between-test duration [28]. In addition, the lack of a control group (healthy volunteers) in the experimental design makes it difficult to determine if this cohort of individuals with schizophrenia had underlying selective attention deficits in comparison to the general population prior to the commencement of treatment. The only other studies to investigate the efficacy of CBD to treat cognitive deficits associated with schizophrenia were conducted in a preclinical schizophrenia model of N-methyl-D-aspartate (NMDA) receptor hypofunction, using the antagonist MK-801 [29, 30]. A study conducted by Deiana et al [29] administered CBD (5, 12 or 30 mg/kg) 30 minutes prior to MK-801 administration (0.08 mg/kg) and then tested social recognition memory in male Wistar rats. Acute pre-treatment with CBD did not prevent the MK-801-induced deficits in social recognition memory, while CBD administration to control rats had no significant effect on social recognition [29]. In another MK-801 (1 mg/kg) study, mice were administered CBD for 22 days then subjected to the Novel Object Recognition (NOR) test [30]. The discrimination index (measured as the ratio of time spent exploring the novel object to the

total time spent exploring either the novel or familiar objects) was significantly higher in MK-801-treated mice administered 60 mg/kg CBD compared to controls, while 30 mg/kg CBD had no significant effect on the discrimination index [30]. As rodents have a natural tendency to explore novel objects, a reduction in the discrimination index demonstrates impaired object recognition memory [31]. Therefore, the results of these two studies suggest that high doses of CBD can alleviate object recognition memory dysfunction, but not social recognition memory in the MK-801 rodent model of schizophrenia.

3.1.2 Effects of CBD on cognitive function in Alzheimer's disease

The therapeutic efficacy of CBD to treat cognitive deficits has also been examined in four studies using neurodegeneration rodent models of Alzheimer's disease (AD) [32-35] (Table 2). A study conducted by Martin-Moreno et al. [32] used intraventricular injection of β-amyloid (Aβ) to model AD, as Aβ plaque formation in the brain is a characteristic feature of AD pathogenesis. Aβ-injected mice displayed increased latency times to find a hidden platform in the Morris Water Maze, indicating impairment to spatial memory [32]. Conversely, Aβ-injected mice administered CBD (20mg/kg) had latency times similar to controls, suggesting that CBD attenuates Aβ-induced deficits in spatial learning and memory [32]. Iron accumulation in the brain is also implicated in the pathogenesis of AD and administration of iron to rodents during the neonatal period mimics the persistent memory deficits observed in Alzheimer's patients in the clinic [33]. Male rats subjected to iron-overload during postnatal days 12-14 had a significantly lower recognition index during the NOR test compared control rats, indicating impaired recognition memory [33]. Acute CBD administration (10 mg/kg) significantly increased the recognition index of iron-overload rats compared to the vehicle controls, while chronic (2 weeks) CBD administration restored recognition memory in iron-overload rats in both the 5 mg/kg and 10 mg/kg dosage groups [33]. Two studies used a double transgenic mouse model of AD that co-expresses two of the three mutant genes implicated in familial AD pathogenesis, amyloid precursor protein (APP) and presenilin 1 (PS1) [36], and exhibits accelerated amyloid pathology and deficits in object and social recognition memory [34, 35]. Chronic CBD administration (20 mg/kg) in APPxPSI mice significantly increased the time spent interacting with the novel object in the NOR test compared to vehicle-treated APPxPSI mice [34], demonstrating improved recognition memory in the CBD-treated mice. In the Social Preference test (which assesses social recognition memory based on the fact that rats prefer to interact with unfamiliar rats) all groups except the vehicle-treated APPxPSI mice demonstrated a preference for the novel rat, suggesting that CBD administration restores social recognition memory in this AD model [34]. On the other hand, CBD treatment did

not affect associative learning in this mouse model of AD, as evidenced during the Fear Conditioning paradigm [34]. A subsequent long-term study (8 months) conducted by the same group investigated the ability of CBD to prevent cognitive deficits associated with AD using the double transgenic APPxPSI mouse model [35]. CBD (20 mg/kg) was administered daily for 8 months, after which time mice underwent a series of behavioural tests (Fear Conditioning Paradigm, Social Preference Test and the Elevated Plus Maze) [35]. The authors confirmed their previous finding of improved social recognition memory with chronic CBD administration, demonstrating that CBD is able to prevent the social recognition memory deficits of AD, but not associative learning deficits [35].

3.1.3 Conclusions

The only clinical trial to investigate the efficacy of CBD to treat cognitive dysfunction in a neuropsychiatric disorder did not find any acute treatment effects of CBD on attention in the Stroop Colour Word test in schizophrenia patients [28]. On the other hand, the two preclinical reports showed that CBD attenuated object recognition memory deficits in an NMDA receptor hypofunction model of schizophrenia, with no effect on social recognition memory [29, 30]. Further research is required to investigate the potential of CBD to improve cognitive deficits in schizophrenia following a long-term CBD treatment period. In addition, to fully ascertain the potential benefits of CBD treatment on cognition in schizophrenia, further studies using tests that align with MATRICS are required. Several preclinical models demonstrate improved recognition, social recognition and spatial memory in AD paradigms following acute and chronic CBD treatment [32-35]. These results may have important implications for the treatment of neurodegenerative disorders; however, extensive randomised, controlled clinical trials are needed to confirm that findings translate to human patients.

3.2 Effects of CBD on cognition in healthy and drug-induced states

Eight studies explored the impact of CBD on cognitive function influenced by cannabis, while no studies have explored the effect of CBD on cognition in other drug-induced states (e.g. opioid, amphetamine, nicotine, alcohol). Two studies examined the influence of CBD on cognitive function in cannabis users during an intoxicated and un-intoxicated state (using their preferred cannabis strains) [37, 38] (Table 1), while 4 studies investigated the effects of CBD on cognitive function following Δ^9-THC administration to human participants [39, 40] (Table 1), rats and monkeys [41, 42] (Table 2). Three studies examined the effect of CBD on cognition following administration of standardised cannabis extracts to human participants [43-45] (Table 1). Lastly, three

studies investigated the effect of CBD alone on cognitive function in healthy participants [46] (Table 1) and rats [47, 48] (Table 2).

3.2.1 Effects of CBD on cognitive functioning in cannabis users

The relative ratio of Δ^9-THC and CBD varies greatly in cannabis strains, particularly with the introduction of high potency (high Δ^9-THC) strains to the market, such as sinsemilla or 'skunk' (20% Δ^9-THC: <0.5% CBD) that contain virtually no CBD (compared to previous strains that contained a 2:1 ratio of Δ^9-THC:CBD) and are associated with a higher risk of psychosis [49]. Morgan et al [37] investigated the relationship between the CBD content of cannabis strains and cognitive functioning of users. Cannabis users were divided into two groups based on CBD content, ie: low (<0.14%) and high (>0.75%) CBD content groups (n=22 per group), based on sample analysis of the self-provided cannabis that participants smoked during this naturalistic study [37]. Participants were tested on verbal and category fluency, prose recall and source memory to assess verbal and episodic memory [37]. This cognitive testing was conducted on two separate occasions: in either drug-free or acutely intoxicated states. During acute intoxication, users of low CBD strains performed significantly worse in the Prose Recall Test compared to users of high CBD cannabis strains, while no changes were observed in Source Memory or Verbal and Category Fluency tests [37]. The cannabis sample analysis revealed no difference in Δ^9-THC levels between the two groups; therefore, the results suggest that high cannabis CBD concentrations may be protective against Δ^9-THC-induced verbal memory impairments. It is worth noting that the authors identified differences in other parameters between the high and low CBD cannabis groups, including higher alcohol consumption and lower Wechsler Adult Reading Test scores (reflecting reduced verbal memory ability) in the low CBD group; however, these factors were added as covariates in memory data analyses [37]. In addition, the authors suggested that differences in these other parameters were unlikely to explain the difference in verbal memory between the low and high CBD concentration groups during acute intoxication as performance did not differ between the low and high CBD groups during baseline (unintoxicated) testing [37]. In another study conducted by the same group, the relationship between cognitive function and the ratio of Δ^9-THC to CBD content in plant strains was examined in un-intoxicated chronic cannabis users [38]. Cannabis users were divided into two groups depending on the amount of cannabis they consumed i.e. recreational (n=54) or daily (n=66) users. Cognitive function was tested using Recognition Memory, Prose Recall and Source Memory tests. Additionally, participant hair samples were analysed for cannabinoid content [38]. The two groups were then further subdivided based on the presence or absence of CBD in the hair sample. Individuals

who consumed cannabis strains containing CBD (as evidenced by the presence of CBD in the hair samples) displayed significantly better recognition memory compared to users who consumed cannabis strains with low CBD, regardless of the degree of cannabis use (daily or recreational) [38]. The presence or absence of CBD in hair samples did not influence Prose Recall or Source Memory test performance; however, when divided based on frequency of cannabis use, daily users of high Δ^9-THC cannabis strains performed poorly in these tests compared to users of low Δ^9-THC strains [38]. These results demonstrate that daily exposure to high Δ^9-THC cannabis is associated with impaired verbal learning and memory, as well as episodic memory [38]. On the other hand, the presence of CBD in cannabis appears to protect against recognition memory impairment in unintoxicated, chronic daily and recreational cannabis users, but has no influence on verbal learning and memory, or episodic memory [38]. These naturalistic studies suggest that CBD may play a protective role in specific aspects of cannabis-induced cognitive impairment; however, considering the numerous constituents found in cannabis, it is difficult to conclude that any protective effects are wholly attributable to CBD.

3.2.2 Effects of CBD on cognitive function in Δ^9-THC administration studies

The administration of Δ^9-THC is a paradigm that allows investigation of CBD effects on cognition during an intoxicated state while removing the confounding factors associated with natural cannabis, including other cannabis constituents and differing CBD concentrations. For example, Hindocha et al [39] investigated the effects of Δ^9-THC or CBD (administered independently or in combination) on emotional facial recognition in cannabis users with a diagnosis of schizotypy. Participants were divided into groups depending on the extent of cannabis use and schizotypy score (n=12 per group). Participants were randomised to receive Δ^9-THC (8 mg), CBD (16 mg), Δ^9-THC+CBD (8 mg+16 mg) or placebo over 4 drug sessions in a crossover design, with a one week washout period between each session [39]. Participants were presented with faces displaying varying emotional intensity (20-100%), including fearful, angry, happy, sad, surprise and disgust. As expected, the recognition of facial emotion became more accurate with increased intensity across all groups [39]. Administration of Δ^9-THC significantly reduced performance in the Emotional Processing Task when subjects were presented with faces graded at 40% emotional intensity, while administration of CBD with Δ^9-THC improved accuracy of emotion identification compared to the Δ^9-THC only group [39]. Interestingly, CBD administration significantly improved accuracy in the emotional processing task beyond placebo levels [39]. There was no main effect of frequency of cannabis use or schizotypy diagnosis. Therefore, these results demonstrate that CBD enhanced emotional facial recognition and limited the detrimental effects of Δ^9-THC in

cannabis users, regardless of frequency of use or schizotypy score [39]. Another study conducted by Englund et al [40] directly tested the hypothesis that CBD prevents Δ^9-THC-induced cognitive impairment by pre-treating healthy human participants with either CBD or placebo prior to receiving a Δ^9-THC challenge (1.5 mg). CBD-treated subjects performed better in delayed recall (during the Hopkins Verbal Learning Task Revised) compared to the placebo pre-treatment group, indicating that CBD treatment prevents verbal learning and memory deficits produced by Δ^9-THC [40]. In the Digit Span Forward task, which assesses working memory, the placebo pre-treated group performed significantly worse following the Δ^9-THC challenge compared to their corresponding baselines scores [40]. CBD pre-treatment resulted in similar scores to baseline (i.e. prior to the Δ^9-THC challenge), indicating that CBD limited the detrimental effects of Δ^9-THC on working memory [40]. CBD pre-treatment was unable to prevent Δ^9-THC-induced working memory impairment in the Digit Span Reverse task (also measures working memory), as performance was significantly worse in both groups following the Δ^9-THC challenge (CBD and placebo pre-treatment), compared to baseline scores, possibly due to the increased difficulty of this test [40]. Overall, the findings of Englund et al [40] demonstrated that CBD pre-treatment prevents Δ^9-THC-induced deficits in verbal learning and memory, and specific (but not all) aspects of working memory in humans. A preclinical study conducted by Hayakaya et al [41] investigated treatment effects of various doses of CBD (3, 10 or 50 mg/kg) on cognition in Δ^9-THC pre-treated (1 mg/kg) male mice. Pre-treatment with Δ^9-THC impaired mouse performance in the Eight-arm Radial Maze, demonstrating impaired spatial learning and memory [41]. Low doses of CBD (3 mg/kg) restored performance in this test to control levels [41], demonstrating that CBD can improve Δ^9-THC-induced deficits in spatial learning and memory. On the other hand, high doses of CBD (50 mg/kg) significantly increased the number of incorrect entries compared to vehicle administration following Δ^9-THC pre-treatment. Interestingly, high doses of CBD administered alone did not impair performance in the Eight-arm Radial Maze, suggesting that CBD may potentiate the detrimental effects of Δ^9-THC on spatial learning and memory when administered to mice at high doses [41]. Indeed, a previous study demonstrated that pre-treatment with high doses of CBD increased Δ^9-THC concentrations in the blood and brain of rats [50], suggesting that a potential mechanism by which high dose CBD enhances Δ^9-THC-induced cognitive impairment may be through altered Δ^9-THC metabolism. A study conducted by Wright et al [42] examined the effects of CBD on cognition in male Rhesus monkeys following acute Δ^9-THC pre-treatment. The CBD/Δ^9-THC group performed significantly better on the Visuospatial Paired Associates Learning task, which assesses visual learning and memory, compared to the vehicle-treated Δ^9-THC group [42]. In addition, CBD limited Δ^9-THC-induced deficits in procedural learning, as evidenced during the Rotating Turntables task

[42]. Conversely, CBD did not improve the Δ^9-THC-induced deficits in spatial working memory in the Self-Ordered Spatial Search task. In fact, the CBD treatment group performed significantly worse compared to the control group (no Δ^9-THC) [42].

3.2.3 Effects of CBD on cognitive function using standardised cannabis extract

The administration of standardised cannabis extracts (containing a defined ratio of Δ^9-THC to CBD) with appropriate control groups (either Δ^9-THC or CBD only groups) has also been employed as a paradigm that allows investigation of CBD treatment effects on cognition. For example, Roser et al [43] examined the effects of acute standardised cannabis extract (10 mg Δ^9-THC+5.4 mg CBD) or Δ^9-THC (10 mg) administration in healthy volunteers. Participants were asked to perform the Choice Reaction task, which assesses selective attention, while the amplitudes of auditory P300 event-related potentials were observed. In this paradigm, a sequence of repetitive tones was randomly interrupted by a tone with a different frequency, to elicit an auditory evoked P300 wave, a cognitive event-related potential (i.e. an electrophysiological response) that is measurable using electroencephalography (EEG). Reduced amplitudes of P300 waves are consistently found in schizophrenia patients, indicating deficient attention and working memory [43]. Reaction times in the Choice Reaction task did not differ between the cannabis extract and Δ^9-THC groups; however, both the cannabis extract and Δ^9-THC only groups displayed reduced P300 wave amplitudes compared to the placebo group, indicating that CBD was not able to attenuate deficits induced by Δ^9-THC in this paradigm [43]. In another study, Schoedel et al [44] investigated the effects of the oromucosal spray Sativex® (GW Pharmaceuticals Ltd. Salisbury, UK) and dronabinol (synthetic THC: Marinol, Solvay Pharmaceuticals, Brussels, Belgium) on the cognitive performance of recreational cannabis users. Participants were administered Sativex® of varying doses (10.8 mg Δ^9-THC+10 mg CBD; 21.6 mg Δ^9-THC+20 mg CBD; and 43.2 mg Δ^9-THC+40 mg CBD), or dronabinol (20 mg and 40 mg Δ^9-THC), or placebo (control) and asked to perform several tests of attention and working memory (Choice Reaction Time task, Divided Attention test and the Short-Term Memory test) [44]. No significant effects of treatment were observed in the Choice Reaction Time or Divided Attention tasks; however, high dose dronabinol (40 mg) significantly increased Short-Term Memory test reaction time compared to the placebo [44]. This result was not observed with Sativex® containing both Δ^9-THC and CBD suggesting that CBD attenuated the detrimental effect of high dose Δ^9-THC on working memory performance in that study [44]. Further evidence that cannabis medicinal extracts do not impair cognition was reported by Wade et al [45], who found that administration of medical cannabis (2.5 mg Δ^9-THC+2.5 mg CBD) or CBD alone (2.5 mg) to

multiple sclerosis patients did not affect their performance on the Short Orientation Memory Concentration (SOMC) test compared to placebo, while administration of Δ^9-THC (2.5 mg) alone did impair performance.

3.2.4 Effects of CBD alone on cognitive function in healthy models

A study conducted by Bhattacharyya et al [46] investigated the effects of Δ^9-THC (10 mg), CBD (600 mg) or placebo on brain activity using neuroimaging techniques (functional magnetic resonance imaging, fMRI) in healthy volunteers while performing cognitive tasks (Verbal Memory task to assess verbal learning and memory, Viewing Fearful Faces task to assess social recognition and Response Inhibition tasks to assess executive function). Interestingly, neither Δ^9-THC nor CBD had any effect on cognitive task performance compared to the placebo [46]; a result that coincides with observations in healthy male Sprague-Dawley rats where acute CBD administration had no effect on spatial learning and memory in the Eight-arm Radial Maze [47]. In addition, Ward et al [48] found that acute CBD administration (2, 5 or 20 mg/kg) to female C57Bl mice 30 minutes prior to performing an AutoShaping task had no effect on conditioned learning. Contrary to the lack of change in behavioural data reported by Bhattacharyya et al [46], they reported also that Δ^9-THC and CBD had opposite effects on regional brain activation while the tasks were being performed [46]. In contrast to Δ^9-THC, CBD augmented striatal, anterior cingulate, medial and lateral prefrontal cortical activation during the Verbal Memory task. CBD also increased activation in the parahippocampal gyrus, left insula and caudate nucleus during the Response Inhibition task, while Δ^9-THC attenuated activity relative to the placebo [46]. In the Viewing Fearful Faces task, CBD attenuated amygdala activation, which the authors suggest may be due to the anxiolytic properties of CBD [46]. While the 600 mg dose of CBD that was utilised by Bhattacharyya et al [46] had no apparent effect on cognition in healthy volunteers, it is interesting to note the contrasting brain region activation observed between the CBD and Δ^9-THC treatment groups and further investigation into the functional implications of the result are warranted.

3.2.5 Conclusions

There is a disparity between studies investigating the effects of CBD on cognitive performance in cannabis users in an intoxicated state and following Δ^9-THC challenge. In cannabis-induced cognitive impairment, CBD attenuates deficits in episodic and recognition memory, and verbal learning and memory; however, these beneficial effects vary depending on the duration (acute use vs. chronic use) and frequency (recreational vs. daily) of cannabis use [37, 38]. The results of Δ^9-THC challenge studies suggest that CBD can improve visual

learning and memory, and procedural learning performance [42], while preventing Δ^9-THC-induced impairments to verbal learning and memory, and improve some working memory tasks during a Δ^9-THC challenge [40], with no effect on spatial learning and memory during Δ^9-THC challenge [41]. In contrast, studies investigating the effects of standardised cannabis extracts found no significant effect of CBD on cognitive performance [43, 44], demonstrating that the one-to-one ratio of Δ^9-THC to CBD has no detrimental effects on cognition [44]. In addition, pure CBD administered to healthy human participants and rats has no effect on cognition [46-48]. There is some crossover in cognitive improvements between human cannabis and Δ^9-THC challenge studies; however, inconsistencies in dosage between these studies pose difficulties in direct comparison of treatment effects. On that note, it is important to consider dosage differences between these studies, i.e. the ratio of CBD to Δ^9-THC in the Δ^9-THC challenge studies in humans (16 mg CBD: 8 mg Δ^9-THC) differed to the ratios in *Cannabis sativa* strains (1.5% CBD: 12-18% Δ^9-THC) [49]. The levels of Δ^9-THC used to induce cognitive impairment (preclinical: 0.5, 1.0 mg/kg; clinical: 1.5 mg and a higher dose of 8 mg) and the dose of CBD used in clinical (16 mg and 600 mg) and preclinical studies (0.5, 1, 3, 10 and 50 mg/kg) varied. Future preclinical studies investigating the effects of CBD treatment should consider the translation of CBD doses in animals to human doses, as low doses of CBD in mice had beneficial effects on cognition, whilst high CBD doses enhanced the detrimental effects of Δ^9-THC on cognition, possibly by impairing Δ^9-THC clearance [41]. The bioavailability, peak concentrations and behavioural effects of cannabinoids vary depending on the route of administration [51], which also differed between the studies reviewed in this section (Δ^9-THC and CBD were administered orally [40, 43-46] or inhaled [39] in the clinical studies, while the preclinical studies used intramuscular [42] and intraperitoneal injections [47, 48]). Therefore, due to the differences in dose and route of administration, it is difficult to draw comparisons between the studies. Finally, although CBD is the main non-intoxicating component of cannabis, the plant contains over 70 different cannabinoids and, therefore, only associations can be drawn from studies investigating the effects of cannabis on cognition. Overall, further research is required to elucidate the therapeutic benefits of CBD on cognitive impairment in cannabis users and following Δ^9-THC administration in healthy participants.

3.3 Cannabidiol as a therapeutic intervention for cognitive impairment in neurological disorders

3.3.1 Effects of CBD on cognitive functioning in preclinical brain ischemia models

Two studies have investigated the effects of CBD on cognitive impairment in preclinical models of brain ischemia [52, 53] (Table 2). Ischemic brain injury produces irreversible changes in the brain, including neuronal

damage and apoptosis that result in impaired memory, attention and executive functioning [52, 53]. A study conducted by Pazos et al. [52] investigated the effects of CBD administration on cognition in Wistar rats exposed to hypoxic-ischemic (HI) brain injury after birth, modelled using left common carotid artery electrocoagulation techniques. Rats were administered a single subcutaneous injection of ~~either~~ CBD (1 mg/kg) 10 minutes post-HI induction and were subjected to the NOR test. Vehicle-treated HI rats had less preference for the novel object compared to non-HI (sham) rats [52], indicating impairment to recognition memory in the model. Interestingly, CBD administration attenuated this deficit, returning novel object preference to control (sham) levels [52]. Spatial learning and memory deficits were observed in a similar model of brain ischemia in adult rodents [53]. In a study by Schiavon et al [53], groups of mice were administered either CBD (3, 10 or 30 mg/kg) or vehicle, 30 minutes prior to a bilateral common carotid artery occlusion to induce brain ischemia (or sham surgery for controls). Mice were then treated again with CBD or vehicle 3, 24 and 48 hours post-surgery, and then underwent a Morris Water maze test one-week post-surgery to examine treatment effects on spatial and memory performance [53]. Vehicle-treated ischemic mice took longer to find the submerged platform than control mice, indicating impaired spatial learning and memory in the ischemia model [53]. On the other hand, mice treated with CBD (pre- and post-surgery 3, 10, or 30 mg/kg) had a lower latency to find the platform than vehicle-treated ischemic mice, indicating that CBD prevented the spatial learning and memory deficits induced by ischemia [53]. Taking both ischemia model studies into consideration, CBD appears to have a neuroprotective role and is able to both attenuate and prevent the learning and memory deficits induced by brain hypoxia.

3.3.2 Effects of CBD on cognitive functioning in preclinical hepatic encephalopathy models

Hepatic encephalopathy (HE) is a disorder that occurs due to build-up of toxic substances in the bloodstream during acute and chronic liver failure. HE manifests symptoms such as personality disturbances, impairments to muscular co-ordination, attention and other cognitive deficits [54-56]. In rodents, exposure to the hepatotoxin thioacetamide (TAA) is used to model acute HE [54], while chronic HE is induced by bile duct ligation (BDL) [55, 56]. Three preclinical studies involving HE modelling of cognitive impairment were identified during the literature search. In one study, acute CBD administration (5 mg/kg) improved the performance of TAA mice compared to vehicle-treated TAA mice in the eight-arm maze test, a measure of spatial learning and memory [54]. Another two studies investigated the effects of chronic CBD administration at the same dose (5mg/kg) using a chronic model of HE induced by BDL [55, 56]. Female Sabra mice subjected to BDL displayed a

significantly higher percentage of entries in the Eight-Arm Radial Maze compared to sham-treated mice 3 weeks post-surgery, demonstrating spatial learning and memory impairment in this model [55, 56]. Following 4 weeks of CBD treatment, CBD-treated BDL mice had a lower percentage of errors compared to vehicle-treated BDL mice, indicating that chronic CBD administration improves spatial learning and memory in this model [55, 56]. Likewise, BDL mice performed significantly worse in the T-Maze test compared to the Sham group, while CBD administration increased the number of entries, suggesting improved working memory by CBD in BDL mice [55]. Overall, these results suggest that chronic CBD treatment can attenuate working memory deficits, while improving spatial learning and memory with both acute and chronic treatment in a HE model.

3.3.3 Conclusions

The effect of CBD on cognitive function in neurological disorders has been investigated in preclinical models of brain ischemia and HE. Acute CBD administration improved recognition memory following impairment due to brain ischemia and prevented spatial learning and memory deficits [52, 53]. Acute and chronic CBD administration improved the spatial learning and memory, and working memory deficits induced by HE [54-56]. The evidence investigating the efficacy of CBD to treat cognitive impairment in neurological disorders is limited and further investigation of the apparent neuroprotective effect of CBD is warranted.

3.4 Cannabidiol as a therapeutic intervention in inflammation-based models of cognitive impairment

The link between the immune system and cognition has been well established [4, 57] as inflammatory states, including increased pro-inflammatory signalling, have been linked to cognitive dysfunction [4]. In healthy people, increased levels of pro-inflammatory cytokines (small molecules involved in immune system signalling) have been associated with poor performance in tasks that assess recognition and working memory, attention and executive function; cognitive domains that are affected in schizophrenia [58, 59]. In the current review, three preclinical studies investigated the effect of CBD on cognition using inflammation-based models [60-62] (Table 2). One study used cecal ligation and puncture (CLP) as a model of systemic inflammatory disease (sepsis) that leads to neurological abnormalities including disorientation, lethargy, confusion and coma [60]. The authors assessed the effect of acute and sub-chronic CBD administration on cognitive function and oxidative parameters in male Wistar rats following CLP induction [60]. In the first experiment, rats received an acute injection of CBD (2.5, 5 or 10 mg/kg) immediately after CLP and were sacrificed after 6 hours [60]. In the second experiment, rats received sub-chronic CBD administration (2.5, 5 or 10 mg/kg daily for 9 days) following CLP

induction and were subjected to the Inhibitory Avoidance task, which measures associative learning [60]. Both the vehicle-treated sham rats and CBD-treated CLP rats improved performance between training and test sessions demonstrating a positive learning and memory effect; however, no significant difference was observed in vehicle-treated CLP rats, indicating memory impairment due to sepsis [60]. The improvement in associative learning by CBD treatment was evident not only at the same effective dose used in the HE models (5 mg/kg) [54-56], but also at lower (2.5 mg/kg) and higher (10 mg/kg) doses of CBD. Overall, these results suggest that sub-chronic CBD administration can attenuate the associative learning deficits produced in the CLP-induced sepsis model over a range of doses.

In a study conducted by Barichello et al [61], male Wistar rats were administered a *S.pneumoniae* injection, which is used to model pneumococcal meningitis. Approximately one third of survivors of pneumococcal meningitis infection present with long-term cognitive impairment, including poor performance in memory tasks and generalised 'cognitive slowing' [63], possibly due to the infiltration of pro-inflammatory molecules in the brain [61]. Following pneumococcal meningitis induction, rats displayed impaired associative learning in the Inhibitory Avoidance task, a result that was not apparent in the sham treatment group. Importantly, sub-chronic (9 days) CBD administration (10 mg/kg, but not 2.5 or 5 mg/kg) restored associative learning in the pneumococcal meningitis model of cognitive impairment [61]. Therefore, similar to the CLP-induced sepsis model, sub-chronic administration of CBD can also attenuate the deficits in associative learning produced by pneumococcal meningitis. Campos et al [62] induced cerebral malaria in mice using Plasmodium berghei-ANKA (PbA) infection. Cerebral malaria manifests as seizures, headache, severe cognitive impairment and often results in death in humans [62]. Three days post infection mice were administered CBD (30 mg/kg) or vehicle, followed by treatment with the anti-malarial drug, Artesunate, at the peak of the infection (5 days post infection) [62]. Behavioural testing 5 days post-infection showed that vehicle-treated PbA/Artesunate mice performed significantly worse on the NOR test and Morris Water maze, demonstrating persistent recognition and spatial memory impairments following malaria treatment [62]. On the contrary, PbA/Artesunate mice treated with CBD performed the memory tasks at control levels, indicating that CBD prevents PbA-induced cognitive deficits [62]. Based on these results, the authors suggested that CBD may be a potential adjunctive therapy for the treatment and/or prevention of the neurological deficits that result from cerebral malaria.

3.4.1 Conclusions

Overall, inflammatory-based models of cognitive impairment consistently show that short-term and long-term CBD administration can attenuate deficits in spatial learning and memory, recognition memory and associative learning [60-62], which are cognitive domains affected in schizophrenia, as identified by MATRICS [2]. Given that CBD can improve cognition in preclinical models of inflammation-induced cognitive dysfunction it is reasonable to speculate that CBD may improve cognition in preclinical models of schizophrenia, particularly as growing evidence suggests an underlying immune dysfunction in the pathogenesis of this disorder [4].

4 Potential mechanisms underlying CBD's effects on cognition

The present literature review provides the first systematic analysis of the available clinical and preclinical evidence on the effects of CBD on cognitive function. The limited evidence investigating the impact of CBD on cognitive deficits in neuropsychiatric disorders showed that CBD had no effect on selective attention in schizophrenia outpatients [28], while CBD administration attenuated object recognition memory impairment [30], but was unable to prevent social recognition memory deficits induced by MK-801 administration in rodents [29]. In preclinical models of AD, CBD treatment improved social and object recognition memory, with no effect on associative learning [32-35]. No human clinical evidence of CBD treatment effects on cognition in AD could be located during this literature search. The limited studies conducted in neurological disorders suggest that CBD has therapeutic benefits for spatial learning and memory, and recognition memory deficits induced by hypoxic brain injury [52, 53]. In preclinical models of hepatic encephalopathy, acute and chronic CBD administration improved spatial learning and memory, and working memory impairments [54-56]. CBD administration improved learning and memory function in preclinical models of inflammatory disorders such as sepsis [60], pneumococcal meningitis infection [61] and cerebral malaria [62]. In cannabis users, exposure to CBD attenuated episodic and recognition memory, and verbal learning and memory deficits; however, these beneficial effects varied depending on the duration and frequency of cannabis use [37, 38]. In Δ^9-THC challenge studies, CBD intervention showed improvement in several cognitive domains (visual learning and memory, procedural learning, verbal learning and memory, and working memory tasks) [40, 42]. CBD dosage is particularly important to consider for Δ^9-THC paradigms as low dose CBD had no effect on spatial learning and memory, while high CBD doses potentiated the detrimental effects of Δ^9-THC [41]. Some studies using standardised cannabis extracts showed that CBD limited the detrimental effects of Δ^9-THC on cognitive function [44, 45], while another study reported contrary findings of no effect [43]. Overall, CBD administration appears to improve cognitive deficits in several domains, with no effect on cognitive function outside

pathological and drug-induced states (i.e. healthy humans and animals) [46-48]. The neurobiology of cognition itself is not yet fully understood, but a vast body of evidence demonstrates the involvement of multiple neural networks with complex interactions between various signalling systems [3, 64]. Therefore, it is highly unlikely that CBD's mechanism of action can be wholly attributed to one specific signalling pathway or system. Indeed, the preclinical studies included in this review demonstrate changes in multiple biochemical parameters; such as inflammatory and oxidative stress markers, as well as serotonin and adenosine neurotransmitter signalling, following CBD treatment of cognitive impairment. The role of these systems in the potential mechanisms underlying the effect of CBD on cognitive function is discussed below.

4.1 Effects of CBD on neuroinflammatory markers

Preclinical models of cognitive impairment (see Sections 3.1 to 3.3 of this review) showed that CBD treated cognitive dysfunction in areas of working and recognition memory, associative and spatial learning and memory, and social recognition memory [30, 32-35, 53-56, 60-62]. A number of these preclinical studies also assessed neuroinflammatory markers, including cytokine levels and expression, microglial activation and astrogliosis [32, 55, 56, 61]. Signalling of the pro-inflammatory cytokine, tumour necrosis factor-alpha (TNF-α) was significantly increased in the hippocampus and frontal cortex of preclinical models that exhibited HE or AD-induced spatial learning and memory, working memory and associative learning impairments [32, 55, 56, 61]. Improved spatial learning and memory, as well as working memory following CBD administration has been associated with down-regulated hippocampal TNF-α and tumour necrosis factor-alpha receptor 1 (TNFRSF1) mRNA expression, with no change in cortical expression [32, 55, 56]. On the other hand, another study reported down-regulated TNF-α levels in the frontal cortex but not in the hippocampus following CBD administration and improved associative learning [61]. Conversely, cortical TNF-α mRNA expression did not change in AD rats exhibiting CBD-induced social recognition memory improvements [35]. Therefore, the literature is confounding but does suggest a possible involvement of TNF-α and TNFRSF1 signalling in the mechanisms underlying the ability of CBD to improve specific aspects of cognition. In addition, one study reported that expression of the pro-inflammatory cytokine interleukin-6 (IL-6) in the cerebral cortex was not altered by CBD treatment, suggesting that the spatial learning and memory improvements observed in the AD model may not be related to changes in IL-6 signalling [32]. Overall, caution may prudent when interpreting the TNF-α and IL-6 results as these studies did not examine both protein and mRNA expression levels, which is important because changes in mRNA expression do not always correlate with changes in functional protein levels [65]. Therefore,

to elucidate the role of pro-inflammatory cytokines in the improvement of cognition following CBD treatment, further studies investigating protein and mRNA expression, as well as receptor and downstream signalling pathways in brain regions relevant to the domains assessed by cognitive testing is required.

Studies presented in this review have also investigated the reactivity of immune cells in the brain (such as microglia and astrocytes) in an effort to explain the mechanism of CBD's apparent therapeutic effects on cognitive impairment. In neuroinflammatory states, activation of these immune cells leads to the release of pro-inflammatory cytokines that can ultimately result in neuronal cell death [66]. Several preclinical models of cognitive impairment discussed in this review exhibit altered astrocyte and microglial activation [30, 53, 54]. For example, in the model of brain ischemia an increased number of active astrocytes was observed [54], while CBD treatment reduced the number of activated astrocytes. This finding was observed using glial fibrillary acidic protein (GFAP) immunohistochemistry methods to measure reactive astrogliosis (an abnormal increase in astrocytes in response to neuronal death), whereby the number of GFAP-positive cells provided an index of neuroinflammation [54]. Therefore, these results demonstrate that CBD treatment reduces neuroinflammation in this preclinical model of brain ischemia. Astrogliosis was also observed in the MK-801 model of schizophrenia; however, there was no effect of CBD treatment on GFAP-positive cell number indicating that CBD did not attenuate astrogliosis [30]. On the other hand, increased expression of the microglial activation marker, Iba 1, was observed in MK-801-treated rats, while CBD treatment attenuated microglial activation in the medial prefrontal cortex and CA1 region of the hippocampus, but not in the dentate gyrus [30]. Overall, the results from these studies imply that decreasing the pro-inflammatory immune response may serve as a potential mechanism by which CBD treatment restores cognitive function in pathological states. Considering the robust anti-inflammatory properties of CBD [67], and the evidence that inflammation is implicated in cognitive deficits (as reviewed in [4]), more research along this line of investigation seems imperative.

4.2 Effects of CBD on oxidative stress parameters

Two studies included in the present review investigated the link between oxidative stress and cognitive performance [35, 60]. Oxidative damage to lipids was present in the striatum of cognitively impaired CLP (sepsis) rats, which was determined by measuring the levels of thiobarbituric acid reactive substances (TBARS, a by-product of lipid peroxidation and indicator of oxidative stress) [60]. Striatal TBARS levels were attenuated by acute CBD administration [60]. Furthermore, sub-chronic CBD administration attenuated hippocampal CLP-

induced lipid oxidative damage and decreased protein carbonyl levels (an indicator of protein damage) compared to controls [60]. In contrast, another study found no change in the oxidative stress marker, F_2-isoprostanes, in the hippocampus following long-term CBD administration in a double transgenic mouse model of AD [35]. Overall, these studies suggest a specific effect of CBD on oxidative stress parameters in brain regions implicated in learning and memory; however, the results seem dependent on the pathological state and the oxidative stress marker measured.

4.3 Effects of CBD on neurogenesis and neurotransmission

In addition to increased pro-inflammatory signalling (see Section 4.1.1), a decrease in protein levels and gene expression of brain-derived neurotrophic factor (BDNF), a neurotrophic factor critical for learning and memory, was observed in preclinical models of HE and meningitis [55, 56, 61]. BDNF plays an important role in the maintenance and survival of neurons, as well as the growth and differentiation of new neurons and synapses. CBD administration significantly increased hippocampal BDNF mRNA expression in the HE model [55, 56]. Hippocampal BDNF levels were not affected by induced meningitis; however, levels in the frontal cortex were decreased and this deficit was restored by CBD treatment [38]. Immunohistochemistry and immunofluorescence techniques have confirmed an increase in hippocampal neurogenesis following CBD administration in a rat model of AD [68]. Therefore, these studies suggest that CBD may promote neurogenesis by increasing BDNF levels, changes in which may correlate with improved functional outcomes in cognition; however, further studies are required to confirm.

Several studies presented in this review have also investigated the effects of CBD on serotonin and adenosine signalling, due to the role of these neurotransmitters in cognition and inflammation [54-56]. The adenosine A_2 receptor (A_{2A}A-R) mediates the effects of BDNF on long-term potentiation and synaptic transmission [55]. Co-administration of CBD with the A_{2A}A-R antagonist, ZM241385, to cognitively impaired BDL mice blocked CBD-induced improvements in performance in the Eight-arm Radial Maze [55]. This blockade in performance was concurrent with reduced hippocampal TNF-α 1 receptor expression and elevated levels of BDNF expression [55]. Furthermore, ZM241385 administration had no effect on the cognitive function of Sham or BDL mice that did not receive CBD treatment [55]. The authors suggested that CBD may be an indirect agonist of A_{2A}A-Rs [55]; indeed, another study found that CBD inhibits adenosine uptake from synaptic terminals prolonging the effects of adenosine on its receptors [69]. In addition to adenosine, two preclinical studies included in this

review investigated the influence of CBD on serotonin 5-hydroxytryptamine (5-HT) signalling in the brain in relation to cognition [54, 56]. In a model of HE that exhibited deficits in spatial learning and memory, whole brain 5-HT levels were significantly up regulated compared to controls, while acute CBD administration attenuated this increase in brain 5-HT levels [54]. In addition, 5-HT_{1A} receptor blockade prevented CBD improvements in spatial memory in BDL mice while (paradoxically) decreasing hippocampal TNF-α 1 receptor expression, with no effect on BDNF expression [56]. Overall, these studies suggest an involvement of serotonin 5-HT_{1A} and adenosine A_{2A} receptors in the mechanisms underlying CBD-induced improvements in cognition; however, further research is required.

5 Conclusions and Future Directions

In conclusion, the studies presented in the current review demonstrate that CBD has the potential to limit Δ^9-THC-induced cognitive impairment and improve cognitive function in various pathological conditions. Human studies suggest that CBD may have a protective role in Δ^9-THC-induced cognitive impairments; however, there is limited human evidence for CBD treatment effects in pathological states (e.g. schizophrenia). Preclinical evidence suggests that overall CBD improves functioning in cognitive domains of learning and memory, in both Δ^9-THC-induced and pathological states of cognitive impairment. Importantly, studies generally show no impact of CBD on cognitive function in a 'healthy' model, that is, outside drug-induced or pathological states. Current studies investigating drug-induced or pathological states of cognitive impairment, lack consensus on basic experimental parameters, including effective dose ranges, route of administration, frequency and duration of dosing needed to elicit optimal cognitive outcomes. In terms of schizophrenia, CBD has shown potential to treat the positive and negative symptoms of the disorder in both patients and rodent preclinical models [reviewed in 24]. There is limited evidence investigating the therapeutic efficacy of CBD to treat the cognitive deficits of schizophrenia; however, CBD treatment improves cognitive function in other neurological disorders, neuropsychiatric and neuroinflammatory models of cognitive impairment. Therefore, well-designed, randomised, controlled trials conducted in schizophrenia patients will be essential to fully elucidate the potential of CBD to improve cognitive deficits in this disorder. The assessment of biochemical markers, such as circulating inflammatory (cytokines, chemokines) and oxidative stress markers, would be useful to determine the immune profiles of treated patients and whether this correlates with any CBD-induced improvements in cognition. Furthermore, future preclinical studies investigating the underlying mechanisms of action of CBD would benefit from using a wide range of behavioural tests that align with MATRICS, to cover the range of

cognitive domains impaired in schizophrenia patients. In addition, the use of preclinical models of schizophrenia would assist in understanding the neurochemical signalling pathways that CBD acts upon to exert its effects on cognition function. The overall importance of this area of research is emphasized by the large percentage of patients who experience cognitive deficits, the impact on their lives and the lack of therapeutic agents currently available to treat the cognitive symptoms of schizophrenia. This justifies the need for further research to evaluate the potential of CBD as a new intervention for cognitive impairment in schizophrenia.

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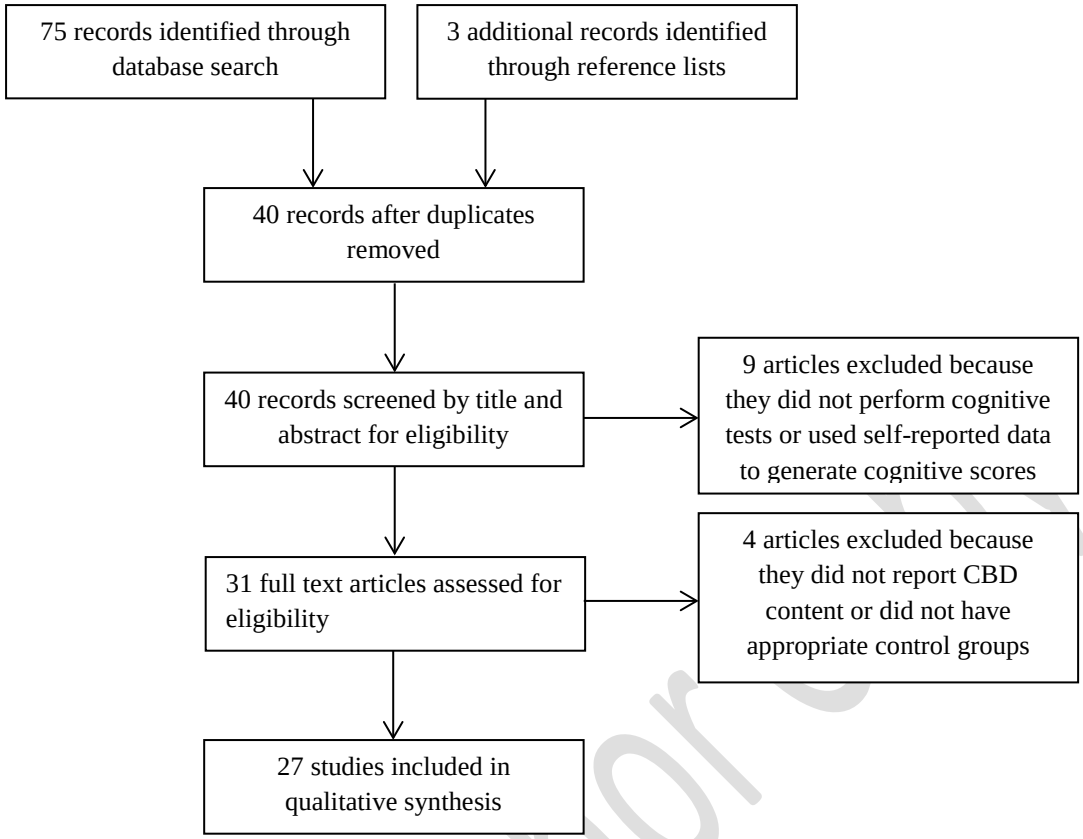

Figure 1: Prisma Flow Diagram for systematic research and identification of studies meeting inclusion criteria (see methods) for systematic review.

Table 1: Clinical studies investigating the effects of cannabidiol on cognition

Author/Year	Study Type	Sample Population/Size	Intervention	Clinical Test	Cognitive Domain	Effect of CBD	
Wade et al. 2003	Double-blind, randomised, placebo-controlled, cross-over	Multiple sclerosis (n=18), spinal cord injury (n=4), brachial plexus damage (n=1) and amputation (n=1)	THC (2.5 mg), CBD (2.5 mg) or cannabis extract (2.5 mg THC+2.5 mg CBD)	Short Orientation Memory Concentration Test	attention	≈	
Roser et al. 2008	Double-blind, placebo-controlled, cross-over	Healthy volunteers (n=20; 10M, 10F)	THC (10 mg), cannabis extract (10 mg THC+5.4 mg CBD) or placebo	Choice Reaction Task	processing speed, attention	≈	
Bhattacharyya et al. 2010	Double-blind, randomised, placebo-controlled, cross-over	Healthy male volunteers (n=15)	THC (10 mg), CBD (600 mg) or placebo	Verbal memory task	verbal memory	≈	
				Viewing fearful faces task	social recognition		
				Response inhibition (Go No-Go)	executive function		
Hallak et al. 2010	Double-blind, placebo-controlled	Schizophrenia outpatients (n=28; 18M, 10F)	CBD (300 mg or 600 mg) vs placebo	Stroop Word Colour	attention	≈	
						DFS	AIS
Morgan et al. 2010	Naturalistic study	Cannabis users (n=134) divided into low (0.08%) vs. high (4.61%) CBD groups	Tested in DFS and AIS (with participant's chosen cannabis)	Prose Recall	verbal memory	≈	↑
				Source Memory	episodic memory	≈	≈
				Verbal category & fluency	executive control	≈	≈
Schoedel et al. 2011	Randomised double-blind, placebo-controlled, cross-over	Recreational cannabis users (n=23; 19M, 4F)	Nabiximols (10.8mg THC+10 mg CBD, 21.6 mg THC+20 mg CBD and 43.2 mg THC+40 mg CBD) or dronabinol (20 or 40 mg THC)	Choice Reaction Time	processing speed	≈	
				Divided Attention test	attention	≈	
				Short-Term Memory test	working memory	≈	
Morgan et al. 2012	Naturalistic study	Cannabis users (n=120; 89M, 31F) divided into recreational (n=54) or daily users (n=66)	Tested in DFS, hair samples analysed for cannabinoid content (CBD vs. no CBD)	Prose Recall	verbal memory	≈	
				Recognition memory	recognition memory	↑	
				Source Memory	episodic memory	≈	
Englund et al. 2013	Randomised, double-blind, placebo-controlled	Healthy volunteers; CBD (n=22) vs. placebo (n=26)	Pre-treatment with 600 mg CBD or placebo prior to THC challenge (1.5 mg)	HVLTR	verbal learning and memory	↑	
				Symbol Coding	working memory	≈	
				NAB mazes	executive function	≈	
				Digit Span Forward	working memory	≈	
				Digit Reverse	working memory	≈	
Hindocha et al. 2015	Randomised, double-blind, placebo-controlled, cross-over	Cannabis users (n=48; 34M, 14F), divided into light (n=24) and heavy (n=24) users	Δ^9-THC (8 mg), CBD (16 mg), Δ^9-THC+CBD (8 mg +16 mg) or placebo	Emotional processing task	social recognition	↑Δ^9-THC+CBD vs. Δ^9-THC ↑ CBD vs. placebo	

Abbreviations: n – number; M – male; F – female; CBD – cannabidiol; THC - tetrahydrocannabinol; HVLTR – Hopkins Verbal Learning Task Revised; DFS – drug-free state; AIS – acute intoxication state; IR – immediate recall; DR – delayed recall; NAB – Neuropsychological Assessment Battery; '↑' - significant improvement in cognition with CBD administration; '≈' – no change in cognition with CBD administration; '↓'– significant impairment in cognition with CBD administration

Table 2: Preclinical studies investigating the effects of cannabidiol on cognitive function

Author/Year	Sex	Strain/Species	Experimental Paradigm		Behavioural test	Cognitive domain	CBD dose (mg/kg)											
							0.5	1.0	2.0	2.5	3.0	5.0	10	12	20	30	50	60
Lichtman et al. 1995	M	Sprague-Dawley rats	Healthy rats administered cannabinoids (WIN-55, 212-2, CP-55, 940, anandamide, CBD)		Radial arm maze	Spatial			≈									
Hakawaya et al 2008	M	ddY mice	Δ^9-THC challenge (1 mg/kg)		Eight-arm maze	Spatial					≈		≈				↓	
Magen et al. 2009	F	Sabra mice	Hepatic encephalopathy via BDL		Eight-arm maze	Spatial						↑						
					T-maze	Working						↑						
Magen et al. 2010	F	Sabra mice	Hepatic encephalopathy via BDL		Eight-arm maze	Spatial						↑						
Cassol-Jr et al. 2010	M	Wistar rats	Sepsis via CLP		Inhibitory avoidance	Associative				↑		↑	↑					
Avraham et al. 2011	F	Sabra mice	Hepatic encephalopathy via TAA (200 mg/kg)		Eight-arm maze	Spatial						↑						
Martin-Moreno et al. 2011	F/M	C57Bl/6 mice	Aβ intraventricular injection AD model		MWM	Spatial									↑			
Barichello et al. 2012	M	Wistar rats	Meningitis model		Inhibitory avoidance	Associative				≈		≈	↑					
Fagherazzi et al. 2012	M	Wistar rats	AD via iron overload (30 mg/kg iron)	Acute	NOR	Recognition						≈	↑					
				Chronic								↑	↑					
Pazos et al. 2012	F/M	Wistar rats	Hypoxic ischaemic injury via electrocoagulation		NOR	Recognition		↑										
Wright et al. 2013	M	Rhesus monkey	Δ^9-THC challenge (0.5 mg/kg)		vsPAL	Declarative	↑											
					SOSS	Spatial	≈											

				RTT	Procedural	≈							
Cheng et al. 2014	M	AβPPxPSI mice	AβPPxPSI double transgenic AD model	NOR	Recognition						↑		
				Social Preference	Social recognition						↑		
				Fear Conditioning	Associative						≈		
Cheng et al. 2014	M	AβPPxPSI	AβPPxPSI double transgenic AD model	Social Preference	Social recognition						↑		
Schiavon et al. 2014	M	Swiss mice	Hypoxic ischaemic injury via BCCAO	MWM	Spatial learning			↑		↑		↑	
Ward et al 2014	F	C57Bl/6 mice	Healthy rats	Autoshaping task	Associative		≈		≈		≈		
Campos et al. 2015	F	C57Bl/6 mice	CM via PbA + antimalarial Artesunate (32mg/kg)	NOR	Recognition							↑	
				MWM	Spatial							↑	
Deiana et al. 2015	M	Wistar rats	MK-801 (0.08 mg/kg) model of schizophrenia	Social Preference	Social recognition				≈		≈	≈	
Gomes et al. 2015	M	C57Bl/6 mice	MK-801 (1 mg/kg) model of schizophrenia	NOR	Recognition							≈	↑

Abbreviations: F – female; BDL – bile duct ligation; CBD – cannabidiol; M – male; CLP – cecal ligation and puncture; TAA – thioacetamide; AD – Alzheimer's disease; MWM – Morris Water Maze; NOR – novel object recognition test; Δ^9-THC - Δ^9-tetrahydrocannabinol; vsPAL – visuospatial paired associate learning task; SOSS – self-ordered spatial search task; RTT – rotating turntables task; BCCAO – bilateral common carotid artery occlusion; PAC – paclitaxel; CM – cerebral malaria; PbA – Plasmodium berghei-ANKA; '↑' - significant improvement in cognition with CBD administration; '≈' – no change in cognition with CBD administration; '↓' – significant impairment in cognition with CBD administration

Supplementary Table 1: Characteristics of studies excluded from the systematic review

Author/Year	Journal of publication	Database	Type of study	Study design	Reason for exclusion
da Silva et al. 2014 [71]	Molecular Neurobiology	Web of Science	Experimental rat model (male Wistar rats)	Chronic CBD administration for 14 days to rats subjected to neonatal iron overload as a model of neurodegenerative disorders. Western blot and real-time PCR analysis of brain proteins associated with mitochondrial fusion and fission mechanisms.	No behavioural tests were performed to assess cognition.
Liput et al. 2013 [72]	Pharmacology Biochemistry and Behaviour	Scopus	Experimental rat model (male Sprague-Dawley rats)	Acute CBD intervention via transdermal delivery vs. i.p. in rats submitted to alcohol-induced neurodegeneration. Assessed neuron degeneration via Fluoro-Jade B staining methods.	No behavioural tests were performed to assess cognition.
Long et al. 2012 [73]	PLoS ONE	Scopus	Experimental mouse model (female C57Bl/6 mice)	Acute and long-term CBD intervention (dose) in a Nrg1 HET mouse model of schizophrenia	No behavioural tests were performed to assess cognition (data on NORT testing was not reported).
Aragona et al. 2011 [74]	Clinical Neuropharmacology	Scopus, Medline	Double-blind, randomized, placebo-controlled, parallel group cross-over trial	Intervention with cannabis extract Sativex (1:1 ratio of Δ^9-THC: CBD) in cannabis-naïve MS patients (n=17). Assessed on PASAT (measures attention and information processing) and self-reported measures of symptoms, quality of life, anxiety and fatigue.	No groups to control for Δ^9-THC or CBD effects alone (only Sativex vs. placebo).
Bergamaschi et al. 2011 [75]	Neuropsychopharmacology	Scopus, Medline	Double-blind, placebo-controlled	Drug-naïve Social Anxiety Disorder patients received either CBD (600mg) or placebo 1.5h prior to the SPST, vs. healthy controls (no medication). Assessed physiological measures and subjective scores on the VMAS and SSPS-N.	No behavioural tests were performed to assess cognition.
Lafuente et al.2011 [76]	Paediatric Research	Scopus	Experimental newborn piglet model	CBD intervention (0.1 mg/kg) 15 and 240 min post-HI induction in newborn piglets. Assessed neurophysiological and neurobehavioral scores and performed histological and biochemical analyses.	No behavioural tests were performed to assess cognition.
Winton-Brown et al. 2011 [77]	Neuropsychopharmacology	Web of Science	Double-blind, pseudo-randomized, cross-over design	Acute intervention with Δ^9-THC (10 mg), CBD (600 mg) or placebo to healthy volunteers (n=14). Assessed cannabinoid blood levels, physiological parameters, psychopathology, sensory stimulation task.	No behavioural tests were performed to assess cognition.
Juckel et al. 2007 [78]	Schizophrenia Research	Scopus, Medline	Prospective, double-blind, placebo-controlled, cross-over	Intervention with Δ^9-THC alone or standardised cannabis extract (Δ^9-THC + CBD) in healthy volunteers (n=22) and assessed effects on MMN amplitudes.	No behavioural tests were performed to assess cognition.
Niyuhire et al. 2007 [79]	Journal of Pharmacology and Experimental Therapeutics	Web of Science	Experimental mouse model (male C57BL/6 mice)	Intervention with marijuana (50, 100 or 200 mg), Δ^9-THC (1, 3 or 10 mg/kg) or placebo and tested in the Morris water maze (spatial learning and memory).	Did not use standardised cannabis extract, level of CBD unknown.

Ilan et al. 2005 [80]	Behavioural Pharmacology	Scopus, Web of Science	Double-blind, placebo-controlled, mixed between and within-subjects design	Intervention with marijuana cigarettes containing Δ^9-THC (high or low) with CBC (high or low) and CBD (high or low) in healthy cannabis users (n=23). Assessed physiological measures (blood pressure, heart rate), cognitive test battery (word presentation, working memory and word recognition tasks), EEG recording.	Use of CBC in paradigm without a CBD only group – cannot determine if effects are due to CBD.
Wade et al. 2004 [81]	Multiple Sclerosis	Scopus, Web of Science, Medline	Multi-center, double-blind, randomised, placebo-controlled, parallel group trial	Intervention with CMBE: Δ^9-THC+CBD (ratio of 1:1, 2.5 – 120mg, daily) in MS outpatients (n=160). Recorded VAS of symptoms, disability, mood, cognition, sleep and fatigue.	No groups to control for Δ^9-THC or CBD effects alone (only Sativex vs. placebo).
Guy et al. 2003 [82]	Journal of Cannabis Therapeutics	Scopus	Partially randomised, placebo-controlled, cross-over trial	Intervention with whole-plant extracts of Δ^9-THC, CBD, Δ^9-THC: CBD (1:1 ratio) and placebo to assess tolerability of sublingual drops, sublingual aerosol or inhalation delivery methods to healthy subjects (n=6). Assessed pharmacokinetics and self-reported symptoms, well-being, intoxication scores, mood and cognition, and adverse event scores.	No behavioural tests were performed to assess cognition.
Leweke et al. 2000 [83]	Pharmacology Biochemistry and Behaviour	Scopus, Medline	Double-blind, crossover trial	Intervention with nabilone (1 mg) and CBD (200 mg) on binocular depth inversion in male human volunteers (n=9). Assessed subjective measures of mood, anxiety and vividness of imagery.	No behavioural tests were performed to assess cognition.